IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Hisakazu KATSUKI *et al.*

Application No. 10/588,609

TITLE: ED-71 PREPARATION

Examiner: Sabiha Naim Qazi

Art Unit: 1612

BRIEF ON BEHALF OF APPELLANTS UNDER 37 CFR §41.37

Anne M. Kornbau
Reg. No. 25,884
Attorney for Appellants

BROWDY AND NEIMARK, P.L.L.C.
624 Ninth Street, N.W.
Washington, D.C. 20001
Phone: (202) 628-5197
Facsimile: (202) 737-3528
E-mail: mail@browdyneimark.com

Attorney Docket: KATSUKI=2

Date: August 30, 2010

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

Rules

BRIEF ON BEHALF OF APPELLANTS UNDER 37 CFR §41.37

The present appeal is taken from the Action of the Examiner mailed December 29, 2009, in finally rejecting claims 10, 12-14, 17 and 18. Furthermore, claims 10, 12-14 and 17-19 stand rejected in the Advisory Action mailed April 2, 2010.

A clean copy of these claims, double-spaced, appears in the Appendix to this Brief.

REAL PARTY IN INTEREST

The real party in interest is Chugai Seiyaku Kabushiki Kaisha, Kita-Ku, Tokyo, Japan.

RELATED APPEALS AND INTERFERENCES

Undersigned is aware of no related Appeals or Interferences.

STATUS OF CLAIMS

Claims 1-9, 11, 15 and 16 have been cancelled.

Claims 10, 12-14, 17 and 18 stand rejected in the Final Office Action mailed December 29, 2009. Claims 10, 12-1 and 17-19 stand rejected in the Advisory Action mailed April 2, 2010. It is therefore not clear if claim 19 is under consideration.

The rejections of claims 10, 12-14, 17, 18 and 19 are being appealed.

STATUS OF AMENDMENTS

The amendment filed March 25, 2010, was deemed not to place the application into condition for allowance. The Examiner did not indicate if the amendment would be entered for purposes of appeal, and it is noted that in the Advisory Action mailed April 2, 2010, that newly submitted claim 19 was deemed to be rejected.

SUMMARY OF CLAIMED SUBJECT MATTER

ED-71, (5Z,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10- secocholesta-5,7,10(19)-triene-1,3,25-triol, is a synthetic derivative of active Vitamin D that is a therapeutic drug for osteoporosis. The main degradation products of ED-71 are 6E-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10- secocholesta-5 (10),6,8,9(1)-triene-1,3,25-triol, hereinafter referred to as the "tachysterol form" of ED-71. and a trans form of ED-71, (5E,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10- secocholesta-5,7,10(19)-triene-1,3,25-triol. (specification, paragraphs [0007]-[0011]).

Degeneration of an oily preparation containing ED-71 can be inhibited by adding an antioxidant, particularly dl-α-tocopherol. (paragraphs [0012], [0049]).

A composition containing a standard degradation product of ED-71, (5E,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10- secocholesta-5,7,10(19)-triene-1,3,25-triol can be used to detect degradation products of ED-71 (paragraph [0028]). The amount of (5E,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10- secocholesta-5,7,10(19)-triene-1,3,25-triol produced after 12 months of storage was suppressed to 1% or less (Table 4).

Vitamin D compounds can be synthesized from (5E,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10- secocholesta-5,7,10(19)-triene-1,3,25-triol (paragraph [0033]).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Claims 12, 13 and 18 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner alleges that there is no description of guidance for suppressing the "generation" in the specification; there is no description of "under shading;" and claim 18 is deemed to be new matter.

2. Claims 12 and 13 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner questions the meaning of "generation", "shading", and "improvement."

3. Claims 10, 14, 17 and 18 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Yamauchi, U.S. Patent No. 6,448,421.

4. Claims 10, 14, 17 and 18 have been rejected under 35 U.S.C. §102(b) as allegedly anticipated by Miyamoto, *Chem. Pharm. Bull,.* and Miyamoto *et al.*, US 4,666,634.

5. Claims 10, 12-14, 17 and 18 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Yamauchi, Miyamoto '634 and Miyamoto, *Chem. Pharm. Bull,.* and Chen, WO 03/047595.

ARGUMENT

1. Claims 12, 13 and 18 comply with the written description requirement.

During a personal interview between the undersigned and Examiner Qazi March 23, 2010, it was agreed that "generation" meant "formation", and substituting "formation" for "generation" would overcome the rejection under 35 U.S.C. §112, first and second paragraphs. It was also agreed during the interview that "shading" means "in the absence of light."

Suppressing the generation is described at page 2, last paragraph, as follows:

> Therefore, to produce ED-71 preparations, it is also important in practice to not only enhance the storage stability of ED-71 serving as an active ingredient, but also to suppress the generation of main degradation products.

That is, one feature of the invention relates to suppressing the formation of degradation products, in particular, the formation of trans ED-71 and the tachy form of ED-71.

The specification mentions "under shading" a number of times, and specifically in Tables 2 and 3 on page 27. In these tables, vials of soft capsules containing ED-71 were stored under 30°C 60% RH and [under] shading. That is, the vials were stored away from light, i.e., shaded. There is no specific requirement for temperature.

The Examiner alleges that there is no method for "improvement" in the disclosure. It is respectfully submitted that claim 18 is in standard Jepson form, that is, in United States Patent Law, a Jepson claim is a method or product claim where one or more limitations are specifically identified as a point of novelty, distinguishable over at least the contents of the preamble. They may read, for instance, "A system for storing information having (...) *wherein the improvement*

comprises: ...". The claim is named after the case, *Ex parte Jepson*[1], decided in 1917. Jepson format is described in MPEP §608(m).

In a crowded art, a Jepson claim can be useful in calling the examiner's attention to a point of novelty of an invention without requiring the applicant to present arguments and possibly amendments to communicate the point of novelty to the Examiner.

The specification at paragraph [0019] discusses the advantages of the invention, one of these advantages being the use of the trans form of ED-71 as a material for the synthesis of various types of Vitamin D compounds. Since this is an advantage of the invention, it is clearly an improvement over previous methods of synthesizing Vitamin D compounds.

2. Claims 12 and 13 are definite.

The term "generation" in claim 12 means formation or production. That is, in the presently claimed invention, as described at paragraph [0014], the generation of degradation products, namely, tachysterol and trans ED-71, is suppressed. That is, in the formation of this degradation product during storage of the active ingredient is suppressed.

"Shading," that is, "under shading" in claim 13, means that the composition is stored in the absence of light, *i.e.*, under shade.

The "improvement" in claim 18 is that, in a standard method for synthesizing Vitamin D compounds, the intermediate compound used in the synthesis is (5E,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol.

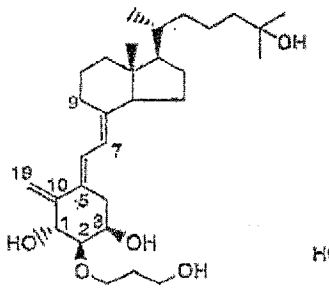
3. Claims 10, 14, 17 and 18 are not anticipated by Yamauchi, US 6,448,421.

---

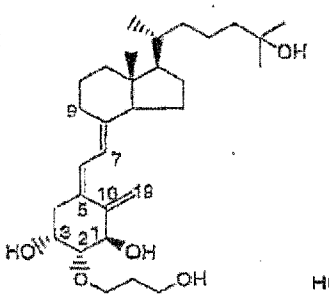
[1] *Ex parte Jepson*, 1917 C.D. 62, 243 O.G. 525

(5Z,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol, ED-71, can decompose to 6E-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10 (19)-triene-1,3,25-triol, the tachysterol of ED-71 and/or to o(5E,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10 (19)-triene-1,3,25-triol, the trans form of ED-71.

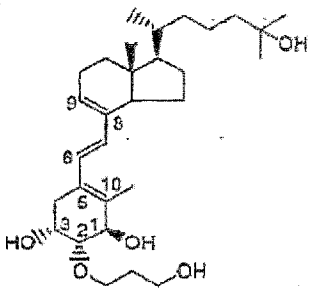
These compounds and their chemical structure are shown in the present specification, for example, at paragraphs [0007]-[0011] and [0028]-[0032]. Their chemical formulas are provided below:



1: Trans form of ED-71
(5E form)



2: ED-71
(5Z form)



3: Tachysterol form of ED-71

As can readily be seen from the chemical formulae, these compounds differ in the configuration at the 5-position or in the location of existing double bonds. Furthermore, these compounds actually exist as separate compounds. For example, each of the compounds can be separated from the other by, for example, chromatography, as shown in Figures 1 and 2 of the present specification.

Yamauchi discloses preparation and purification of ED-71. In contrast thereto, the present claims are directed only to the trans form of ED-71, that is, the 5Z-form. Claim 10 is drawn to a composition containing the trans form of ED-71, and claims 12 and 13 are drawn to a method for suppressing the formation of the trans form. In claim 14, the trans form is used as a standard for the degradation

product. Claim 17 and 18 are directed to methods of synthesizing Vitamin D compounds using the trans form as an intermediate.

As has been discussed at length in the prosecution of these claims, the trans form of ED-71 is a completely different compound from ED-71 itself.

It is believed that the Examiner understands that either of (5Z,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10 (19)-triene-1,3,25-triol or of (5E,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10 (19)-triene-1,3,25-triol recited in the claims is the tachy form of ED-71. This is because the Examiner refers to tachysterol of formula III disclosed in Yamauchi, which she alleges anticipates the claimed invention. However, neither of these two compounds is the tachy form of ED-71. Correctly, (5Z,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10 (19)-triene-1,3,25-triol is ED-71 and (5E,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10 (19)-triene-1,3,25-triol is the trans form of ED-71.

Thus, Yamauchi does not anticipate the herein claimed invention, as Yamauchi does not disclose a method for suppressing the formation of a degradation product of ED-71.

In *Sanofi-Synthelabo, Sanofi-Synthelabo Inc, v. Apotex, Inc.*, 550 F.3d 1075; 89 USPQ2d 1370 (Federal Circuit 2008), the court held that the district court was correct in its holding that the dextrorotatory isomer was patentable in view of its known racemate described in earlier patents. As in the present case, the new isomer has different properties from the known compound. Therefore, it is respectfully submitted that the trans form of ED-71 is patentable over ED-71.

4. Claims 10, 14, 17 and 18 are not anticipated by Miyamoto, *Chem. Pharm. Bull,.* and Miyamoto *et al.*, US 4,666,634.

The Examiner alleges that because the references disclose a method for producing ED-71 they inherently disclose the presently claimed invention.

This rejection is respectfully traversed.

Miyamoto discloses Vitamin D analogues that have a hydroxy group at the 2-position. The presently claimed invention relates to stabilizing preparation containing ED-71 as well as standards for assaying for degradation products of ED-71. The trans form of ED-71, which is the most significant degradation product, can be used both in the analysis of an ED-71 preparation to gauge its stability, and as a material for synthesizing various types of Vitamin D-based compounds.

The trans form of ED-71 and the tachysterol form of ED-71 are not the same compounds disclosed by Miyamoto, and it is not understood how the Examiner can allege that Miyamoto anticipates the herein claimed invention. As noted above, a compound can be patentable over a known isomer of the compound.

5. Claims 10, 14, 17 and 18 are not anticipated by Miyamoto, *Chem. Pharm. Bull,.* and Miyamoto *et al.*, US 4,666,634.

The Examiner alleges that because the references disclose a method for producing ED-71 they inherently disclose the presently claimed invention.

Miyamoto discloses Vitamin D analogues that have a hydroxy group at the 2-position. The presently claimed invention relates to stabilizing preparation containing ED-71 as well as standards for assaying for degradation products of ED-71. The trans form of ED-71, which is the most significant degradation product, can be used both in the analysis of an ED-71 preparation to gauge its stability, and as a material for synthesizing various types of Vitamin D-based compounds (page 6, paragraph [0019]).

The trans form of ED-71 and the tachysterol form of ED-71 are not the same compounds disclosed by Miyamoto, and it is not understood how the Examiner can allege that Miyamoto anticipates the herein claimed invention. As noted above, a compound can be patentable over a known isomer of the compound.

6. Claims 10, 12, 14, 17 and 18 are not unpatentable over Yamauchi, Miyamoto *Chem. Pharm. Bull,*. Miyamoto '634 and Chen, WO 03/047595.

As noted above, neither Yamauchi nor Miyamoto discloses the trans form of ED-71.

The Examiner has cited column 19, lines 35-41, as teaching the products. It appears that column 19, lines 45-50, is the passage that is relevant, which passage states that the tachy and lumi forms and the pro-form of ED-71 are useful for a test or analysis which may be carried out in the synthesis of a Vitamin D derivative. However, this says nothing at all about measuring degradation of ED-71 during storage, nor of the trans form itself.

Chen states at paragraph [0056], "The pharmaceutical compositions of the present invention may further comprise one or more additives. Additives that are well known in the art include, e.g., antioxidants, ..." However, it was general technical knowledge at the time of completion of the present invention that antioxidants are added to suppress generation of oxides, that is, to prevent oxidation of compounds in a system. Thus, one skilled in the art reading Chen would assume that the antioxidants were added to prevent oxidation of Vitamin D compounds.

Miyamoto only discloses compounds of the 5Z form, and Miyamoto fails to disclose any compounds of the 5E form, as claimed herein.

In contrast thereto, the decomposition products to be suppressed in the presently claimed compositions are not oxidation products, the formation of which would be suppressed by antioxidants, but are the trans form of ED-71 and the tachysterol form of ED-71. These decomposition products are not oxides of ED-71, but are isoforms of ED-71. These decomposition products have neither an increased number of oxygen atoms nor a reduced number of hydrogen atoms, which would be the result of oxidation of ED-71. However, it has been demonstrated that dl-α-

tocopherol is far superior to other antioxidants in suppressing summarization of ED-71.

In the supplemental remarks filed March 26, 2008, the Declaration of Hitoshi SATO, one of the inventors of the present application, was submitted. In this declaration, Mr. SATO provided evidence showing that the trans form of ED-71 exhibited a relative differentiation-inducing activity of HL-60 cells that was nearly 20 times greater than the parent compounds, ED-71. It is clear from this declaration that the trans form of ED-71 is not obvious over the parent compounds.

In responding to the remarks made in the amendment filed October 14, 2009, the Examiner alleged that both 5E,7E and 5Z,7E are known, citing WO2005/074943. However, this publication is based on the same priority document as the present application, and one would expect it have all of the same information as in the present specification. Because this publication is based upon the same priority document as the present application, it is respectfully submitted that this publication cannot serve as evidence that the trans form of ED-71 was known.

With respect to the difference between ED-71 and the trans form of ED-71, it is not required that the specification provide evidence of the differences. That is exactly why the declaration of Hisakazu KATSUKI was submitted with the amendment filed August 20, 2009. That declaration demonstrated that that these two compounds have greatly different properties in differentiation. This is all that is required by the *Sanofi* decision cited above to differentiate the trans form of ED-71 from ED-71.

CONCLUSION

Appellants believe and respectfully submit that the Examiner's rejections are without merit for the reasons pointed out above, unreasonable, that no anticipation has been established and that no *prima facie* case of obviousness has been established and that the Examiner has not met this burden. Appellants further respectfully submit that the claims are definite and fully enabled by the specification and the written description.

These rejections should be reversed and such is respectfully prayed.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicants

By: _____
Anne M. Kornbau
Registration No. 25,884

AMK:ltm
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\Y\YUAS\Katsuki2\Pto\2010-08-30 Appeal Brief.doc

CLAIMS APPENDIX

10. A composition comprising a standard degradation product for analysis of a sample containing (5Z,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol, said composition containing as the standard degradation product (5E,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol.

12. A method of suppressing the generation of a degradation product in an oily preparation comprising (5Z,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10- secocholesta-5,7,10(19)-triene-1,3,25-triol, comprising adding dl-α-tocopherol to the preparation, wherein the degradation product is (5E,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol.

13. The method of Claim 12, wherein the amount of (5E,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol generated in the preparation after 12-month storage at room temperature under shading is suppressed to 1% or less.

14. The compound according to Claim 10, which is used as a standard of a degradation product in analysis of a preparation comprising (5Z,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol.

17. A compound of (5E,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol, for synthesizing Vitamin D compounds.

18. In a method for synthesizing a Vitamin D compound comprising reacting an intermediate compound,

the improvement wherein the intermediate compound is (5E,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol.

19. A composition comprising a standard degradation product for analysis of a sample containing (5Z,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol, said composition consisting of, as a standard degradation product, (5E,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol.

EVIDENCE APPENDIX

The attached Declaration Under 37 C.F.R. §1.132 of independent expert Hioshi SAITO, was filed on March 26, 2008, in the U.S. Patent and Trademark Office in Application No. 10/588,609.

The Supplemental Remarks were filed supplemental to the amendment of March 8, 2008, the latter in reply to the non-final Office Action mailed January 8, 2008, and therefore should have been entered as a matter of right as it was filed before the issuance of the Final Action of December 29, 2009. Such Declaration is not referred to at all in the Final Rejection of December 29, 2009.

RELATED PROCEEDINGS APPENDIX

There are no related proceedings in connection with the subject application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Hisakazu KATSUKI et al
Application No.: 10/588,609
Filed: August 7, 2006
For: ED-71 PREPARATION

Confirmation No. 8366
Art Unit: 1616

Examiner: QAZI, SABIHA NAIM

DECLARATION

Honorable Commissioner of Patent and Trademarks
P.O.Box 1450
Alexandria, Virginia 22313-1450

Sir:

I, Hitoshi SAITO, a Japanese citizen, residing at 33-3 Fuji Village, Mishima-city, Shizuoka-prefecture, Japan, hereby solemnly and sincerely declare and state that:

I was awarded M.Sc. in 1989 from the Faculty of Science and Technology, Science University of Tokyo, Chiba-prefecture, Japan;

I have been employed by Chugai Pharmaceutical Co. Ltd., the assignee of the present application, since 1997, and worked at Fuji-Gotemba Research Laboratories in Gotemba, Shizuoka, Japan from 1997, as a researcher of bone biology field during the entire period.

I declare further that I engaged as a researcher in research into vitamin D3 preparations.

I declare further that I have read the Official Action in the above-identified application, and have read, and am familiar with each of the references cited in the Official Action by the Examiner.

Purpose of this declaration

The purpose of this declaration is to show experimental data to establish an advantageous effect of (5E,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol (trans form of ED-71).

I declare that the following tests were conducted at my direction or under my supervision, and that the test results are true and correct to the best of my knowledge.

Materials and Test Method

1. Test Samples

Trans form of ED-71 (lot No.: YM99G045-4-1)

Site of manufacture: Chugai Pharmaceutical Co. Ltd, Synthetic Technology Research Laboratory

Supplier: Chugai Pharmaceutical Co. Ltd, Synthetic Technology Research Laboratory

Supplied form: ethanol solution (1mg/mL)

Storage conditions: in a light-shielding vial, in a freezer at a preset temperature of –20℃ or less

Control 1: 1α, 25-$(OH)_2$-D_3 (lot No.: WVC99AJ87)

Manufacturer: SOLVAY PHARMACEUTICALS

Supplier: Chugai Pharmaceutical Co. Ltd, Chemistry Research Laboratory

Supplied form: ethanol solution (1.02mg/mL)

Storage conditions: in a light-shielding vial, in a freezer at a preset temperature of –20℃ or less

Comments: This substance was selected to show an effect of a representative active vitamin D as a positive control, for comparison with trans form of ED-71.

Control 2: ED-71 (lot No.: 8G03ED)

Site of manufacture: Chugai Pharmaceutical Co. Ltd, Synthetic Technology Research Laboratory

Supplier: Chugai Pharmaceutical Co. Ltd, Synthetic Technology Research Laboratory

Supplied form: powder (25mg)

Storage conditions: in a light-shielding vial, in a freezer at a preset temperature of –20℃ or less

Used form: Before testing ED-71, a ED-71 solution in ethanol (0.93mg/mL)

was prepared, and stored in a light-shielding vial filled with argon gas, in a freezer at a preset temperature of –20℃ or less. Ethanol was selected since it is commonly used as a solvent for vitamin D derivatives.

Comments: ED-71 substance is a parent compound of trans form of ED-71.

2. Cells used

Cells: HL-60 cells

Subculture method: subculture was conducted in RPMI-1640 medium supplemented with 10% of fetal calf serum, at 37℃, in an atmosphere of 5% CO_2 in air.

Storage location: -130℃ freezer

Origin (animal species): human acute myelogenous leukemia cell strain (supplied by Chugai Pharmaceutical Co. Ltd, Pharmaceutical Technology Research Laboratory

3. Experimental Method

HL-60 cells were subcultured in RPMI-1640 medium supplemented with 10% of heat-inactivated fetal calf serum and 20μg/ml gentamycin, at 37℃, in a humidified atmosphere of 5% CO_2 in air.

An ability of induction of differentiation was estimated by the ability of HL-60 cells to generate a superoxide anion.

Each of the solutions of control samples (1α, 25-$(OH)_2$-D_3 and ED-71) and trans form of ED-71 (about 10^{-3} mg/mL) was diluted by use of 10 volumes of RPMI-1640 medium seven times sequentially, to produce sample solutions with a concentration of $1x10^{-10}$-$1x10^{-4}$mg/mL. HL-60 cells were seeded at $1x10^5$cells/mL in a growth media and cultured for 4 days in the presence of various concentrations of the sample solutions, to induce differentiation. Then, the cells were washed free of the compounds, and suspended in a 1.5mL reaction mixture containing 80μM ferricytochrome c (Sigma Chemical Co., St. Louis, MO; Sigma code: C-2506), and 500 ng/mL phorbol myristate acetate (Sigma; Sigma code: P-8139) in 0.1% gelatin Hank's balanced salt solution without phenol red. The mixture was incubated at 37℃ for 60 min, and centrifuged for 10 min. at 400xg at 4℃. The reduction of ferricytochrome c was measured by use of the absorption increase at 550 to 540 nm (molar absorption coefficient, $19.1x10^3$/cm) with a Hitachi U-3200 double-beam spectrometer. The results are shown in Figure 1 and Table 1 below.

Results

Fig 1 Differentiation-Inducing activity on HL-60 cells

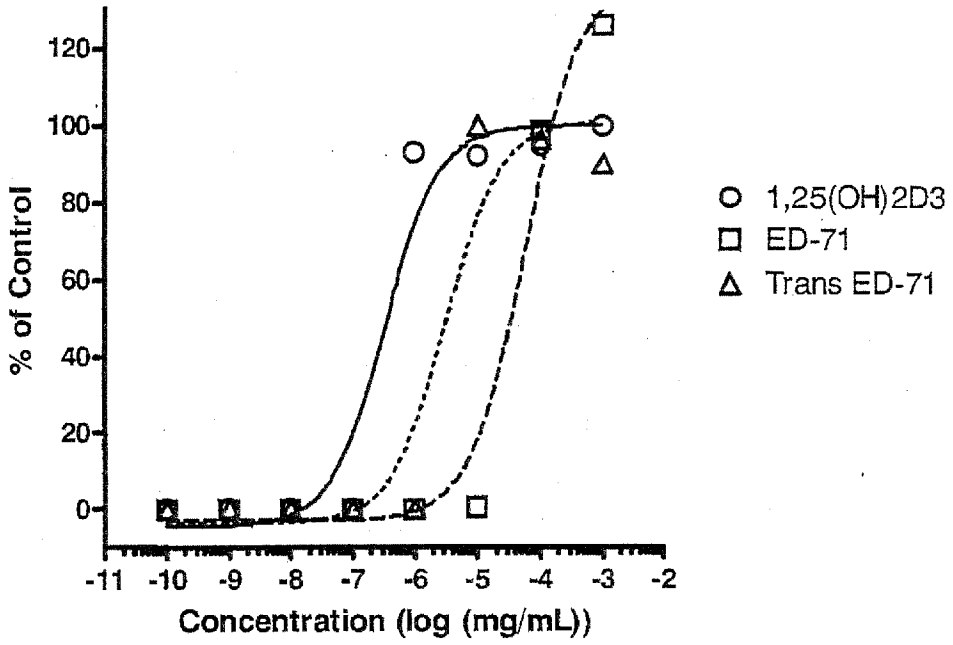


Table 1 Comparison of differentiation-inducing activity on HL-60 cells

Vitamin D derivatives	EC_{50}	Relative differentiation-inducing activity calculated based on 1α, 25-$(OH)_2$-D_3
1α, 25-$(OH)_2$-D_3	4.91×10^{-7}	1
ED-71	5.77×10^{-5}	0.0085
Trans form of ED-71	2.84×10^{-6}	0.1731

As shown in Table 1, trans form of ED-71 showed a relative differentiation-inducing activity on HL-60 cells of 0.1731 (this value was calculated from EC_{50} of the trans form, on the basis of EC_{50} of 1α, 25-$(OH)_2$-D_3, with regarding EC_{50} of 1α, 25-$(OH)_2$-D_3 as "1"). This value is almost 20 times higher than that of the parent compound, ED-71.

Conclusion

Trans form of ED-71 of the present invention shows a differentiation-inducing activity of almost 20 times higher than that of the parent compound, ED-71. I consider that this fact

supports an advantageous effect of the present invention beyond expectations of those skilled in the art. Therefore, I trust that the present invention of trans form of ED-71 is unobvious over the citations.

I declare further that all statements made therein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon..

Dated this 29th day of January, 2008

Hitoshi SAITO

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

		Atty. Docket: KATSUKI2
In re Application of:	)	Conf. No.: 8366
Hisakazu KATSUKI et al.	)	Art Unit: 1616
Appln. No.: 10/588,609	)	Examiner: S. N. Qazi
Filed: August 7, 2006	)	Washington, D.C.
For: ED-71 PREPARATION	)	

DECLARATION UNDER 37 CFR 1.132

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22314

Sir:

I, Hisakazu Katsuki, a Japanese citizen, hereby declare as follows:

1. I received a master's degree in Pharmaceutical Science (Clinical pharmacy course) in March 1995, at Kumamoto University, Kumamoto-shi, Japan.

2. I have been employed by Chugai Pharmaceutical Co. Ltd., the Assignee of this application, since 1995, and I have worked as a researcher for the Ukima Research Laboratories of the Assignee, at Kita-ku, Tokyo, Japan.

3. I have read the Official Action issued against the subject patent application mailed on March 20, 2009 and have noted the Examiner's allegation that Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable

over CHEN et al. (WO 03/047595), MIYAMOTO et al. (US Patent 4,666,634) and Chem. Pharm. Bull. (all 892 references).

4. I, one of inventors of the subject application, conducted the following experiment, in order to evidence that the method of Claims 12 and 13 achieves results greater than those which would have been expected from the combination of the prior arts.

5. The results are true and correct to the best of my knowledge.

Method:

To compare anticxidants, BHA, catechin, tocopherol, ferulic acid, BHT, citric acid, and thiolactic acid, with one another with respect to effectiveness in suppressing generation of (5E,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol (hereinafter referred to as "trans form of ED-71") in an oily preparation containing (5Z,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol (hereinafter referred to as "ED-71"), soft capsules filled with a solution of ED-71 and one of the antioxidants in a medium-chain triglyceride, caprylic/capric triglyceride (commercially available as "MCT(ODO-C)"), were prepared and stored under conditions for accelerated degradation of ED-71. After the storage, the capsules were each analyzed for the amount of trans form of ED-71 formed during the storage.

1) Preparation of soft capsules

ED-71 and one of the antioxidants were dissolved in caprylic/capric triglyceride to prepare a solution containing 1 μg (2 nmol) of ED-71 and 11.9 nmol of the antioxidant per 100 mg of the solution. Then, 100 mg of the solution was injected into an empty soft capsule, the shell of which is composed of 54.71 mg of gelatin, 8.34 mg of D-sorbitol and 1.95 mg of caramel, by means of a syringe with a needle. The capsule was sealed with gelatin.

These procedures were repeated for each of the antioxidants to provide sealed soft capsules containing various types of antioxidant.

2) Storage

The sealed soft capsules were placed into a bottle which was then sealed. The bottle was stored at 40°C for two months.

3) Determination of trans form of ED-71

After completion of storage, the sealed soft capsules were removed from the bottle, and the solutions were extracted from the capsules, and 50-μL aliquots thereof were then subjected to HPLC analysis to determine the amount of trans form of ED-71 formed during the storage.

Column: YMC-Pack ODS AM-303 (250 × 4.6 mm, 5 μm)

Mobile phase: acetonitrile/water =1:1

Flow rate: 1.2 mL/min

Peak detection: 265 nm

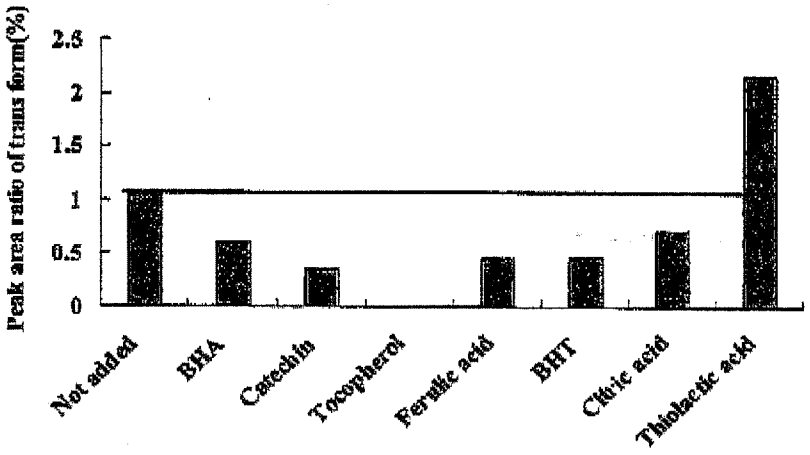
Column temperature: 30°C

Running time: 35 min

A peak area ratio of trans form of ED-71 relative to the total sum of detected peak areas was calculated and used as an index of the amount of trans form of ED-71.

Results:

The figure shown below is a graphical presentation of the results obtained. The lower the level of the bar in the figure, the greater the effectiveness of the antioxidant designated immediately below the bar in suppressing the formation of trans form of ED-71.



As can be seen form the figure, a dramatic effect on the suppression of the formation of trans form of ED-71 is observed when tocopherol is added. Tocopherol is far more effective than the other antioxidants tested, i.e., BHA, catechin, ferulic acid, BHT, citric acid and thiolactic acid.

The results indicate that the effect of the inventive method currently claimed in Claims 12 and 13 where antioxidants are limited to dl-α-tocopherol is greater than that which would have been expected from a combination of the prior arts, and that the effect is of a significant, practical advantage. Such an effect would not have been expected from the disclosures of the prior arts.

Therefore, the currently claimed method is unobvious over the prior arts.

I hereby further declare that all statements made herein are to my own knowledge and belief true, and that all statements made on information and belief are believed to be true, and that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

August 20, 2009 Hisakazu Katsuki

Hisakazu Katsuki